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## **Computer and mobile technology interventions to promote medication adherence and disease management in people with thalassemia (Protocol)**

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# Computer and mobile technology interventions to promote medication adherence and disease management in people with thalassemia

Sherif M Badawy<sup>1</sup>, Kerry Morrone<sup>2</sup>, Alexis Thompson<sup>1</sup>, Tonya M Palermo<sup>3</sup>

<sup>1</sup>Paediatrics, Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago; Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA. <sup>2</sup>Department of Pediatric Hematology Oncology, Children's Hospital at Montefiore, Bronx, New York, USA. <sup>3</sup>Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington, USA

Contact address: Sherif M Badawy, Paediatrics, Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago; Northwestern University Feinberg School of Medicine, 225 E. Chicago Avenue, Box #30, Chicago, Illinois, IL 60611, USA. [SBadawy@luriechildrens.org](mailto:SBadawy@luriechildrens.org).

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To identify and assess the effects of computer and mobile technology interventions designed to facilitate medication adherence and disease management in individuals with thalassemia, including:

1. evaluating the effects of using computer and mobile technology interventions for medication adherence and disease management on health and behavioural outcomes;
2. identifying and assessing the effects of computer and mobile technology interventions specific to different age groups (children, adolescents and adults) and type of modality (e.g. cell phone, the Internet).

## BACKGROUND

Thalassemia syndromes are inherited hemoglobin disorders that result when the synthesis of normal hemoglobin is lacking or significantly reduced ([Martin 2013](#)). Approximately 5% of the world's populations are estimated to carry one variant globin allele with over 300,000 newborns affected every year ([Weatherall 2012](#)).

## Description of the condition

Thalassemia syndromes include either alpha ( $\alpha$ ) thalassemia or beta ( $\beta$ ) thalassemia.  $\alpha$ -thalassemia is caused by either absent or decreased production of  $\alpha$ -globin chains and its clinical severity varies based on the number of alleles affected as well as the type of genetic mutation ([Higgs 2010](#)).  $\beta$ -thalassemia is caused by either absent or decreased production of  $\beta$ -globin chains and its clinical

presentation can be as early as the first six months of life with moderate to severe anemia, or in early childhood with symptoms such as anemia, jaundice, abdominal distention, hepatosplenomegaly and poor growth (Rund 2005). People with  $\beta$ -thalassemia major require blood transfusions on a regular basis, on average 8 to 12 times or more per year. In contrast, those with  $\beta$ -thalassemia intermedia can maintain an adequate hemoglobin level and require packed red blood cell (pRBCs) transfusions only in times of physiologic stress, or fewer than eight times per year (Martin 2013; Rund 2005). For people with thalassemia, stem cell transplantation is the only curative treatment option (Angelucci 2010) and long-term red blood cell transfusion remains the mainstay of therapy, which may lead to iron overload causing severe complications and damage in different body organs (Martin 2013). Long-term iron chelation is essential for people with thalassemia to minimize the ongoing iron loading process (Rachmilewitz 2011; Ware 2013). Three iron-chelating agents, deferoxamine, deferiprone, and deferasirox, are approved by the USA's Food & Drug Administration (FDA) and are commercially available. Routine monitoring may vary with different iron chelators and as a minimum should include serum ferritin levels (every three months) and measurements of cardiac and liver iron burden with annual magnetic resonance imaging (MRI) scans (Badawy 2016a; Martin 2013). Recent studies have shown the need for iron chelation therapies has an impact on the quality of life of people with thalassemia and results in low levels of personal satisfaction (Abetz 2010; Cappellini 2007; Payne 2008; Porter 2012; Taher 2010; Trachtenberg 2012; Trachtenberg 2014). In addition, sub-optimal adherence can increase adverse events associated with iron overload and result in increased morbidity, mortality, healthcare utilization and cost of care (DiMatteo 2002; Sabate 2003; Vekeman 2016).

## Description of the intervention

Mobile technology interventions for promoting medication adherence and disease management include delivery of education, reminders, or behavioural skills through cell (mobile) phones (e.g. text-messaging and mobile applications), the Internet (e.g. web-based interventions), or other mobile technology tools. Mobile technology interventions could:

1. enhance the communication between patients and healthcare providers,
2. facilitate management and self-monitoring of thalassemia;
3. provide education about thalassemia, iron chelators and other related medications;
4. support adherence to iron chelators or medications using reminders;
5. offer a network for communication among patients with thalassemia;
6. support decision making for people with thalassemia and their parents or caregivers; or

7. collect or capture users' data (from the individuals concerned and their parents or caregivers).

We conducted a brief scoping review of the literature in PubMed and found two published studies that used mobile-based interventions to improve adherence to iron chelation in people with thalassemia (Leonard 2017; Ward 2016). The first study by Ward and Taha included 35 people with thalassemia (aged 18 to 34 years), who were part of a Delphi process to inform the development of a mobile app to improve disease self-management, including adherence to chelation therapy (Ward 2016). The research team was able to develop and test the mobile app with participants who perceived it as highly favorable with improved adherence to iron chelation and positive experience using it, especially the adherence pledge functionality and customized treatment goals (Ward 2016). The second study by Leonard included 11 people ( $\beta$ -thalassemia major and sickle cell anemia) receiving chronic blood transfusions and evaluated a mobile app intervention as part of an intensive training program to improve disease self-management, including adherence to iron chelation (Leonard 2017). The authors reported on the feasibility of the mobile app intervention and that there was high acceptability and improved disease knowledge, as well as adherence to iron chelation (using medication possession ration with pharmacy records and laboratory markers of adherence) with serum ferritin levels trending downwards (Leonard 2017).

## How the intervention might work

Mobile technology interventions for promoting medication adherence and disease management could:

- enhance an individual's self-efficacy, organizational skills, or change adherence behaviour (e.g. reminders for daily iron chelators, clinic appointment reminders, transfusion reminders, feedback on adherence to iron chelation therapy);
- provide a form of communication (e.g. health professionals);
- establish social support networks (e.g. advocacy groups, peer-to-peer networks); or
- provide education about thalassemia, iron chelation and necessary steps for optimal disease management.

By increasing self-efficacy (Bandura 1977) and providing support mechanisms (Christakis 2004; Cobb 1976; Cohen 1985), computer and mobile technology health interventions may influence health behaviours and enhance self-management of long-term illnesses. These interventions may facilitate education on self-management problem solving skills, and in this way increase the individual's confidence in carrying out the behaviours necessary to achieve the desired goal of optimum disease management. A recently developed taxonomy of behaviour change techniques (BCT) has been published with 93 consensually agreed, distinct BCTs, which will help to further define specific intervention effects, including mobile technology interventions (Michie 2013).

## Why it is important to do this review

Management of thalassemia represents a challenge for people with the disease and their families (Badawy 2016a; Evangelì 2010). Recent reports demonstrated a high prevalence of poor self-management and non-adherence in thalassemia in both children and adults (Cappellini 2007; Evangelì 2010; Haghpanah 2014; Lee 2011; Porter 2012; Porter 2011; Trachtenberg 2011; Vekeman 2016) similar to other chronic health conditions (Loiselle 2016; Modi 2012; Walsh 2014). Nevertheless, effective self-management is essential to maximize treatment efficacy, optimize clinical outcomes, and reduce unnecessary health care utilization and costs (Modi 2012). However, people with thalassemia and their families are responsible for managing complex and time-consuming treatment regimens, including daily medications (e.g. iron chelators, vitamins, hormonal supplements), laboratory monitoring (e.g. serum ferritin, hemoglobin concentration), imaging studies (e.g. MRI of liver R2\*, MRI of heart T2\*), and attendance at regular transfusions as well as routine clinic appointments with a variety of health care professionals (Badawy 2016a; Rachmilewitz 2011; Rund 2005). These treatment regimens could place substantial burden on individuals with thalassemia and their families, and effective management of these regimens represents a challenge to them. Moreover, in relation to industrialised countries, given that thalassemia predominantly affects individuals who are of ethnic minorities (Rund 2005; Weatherall 2012), disparities in access to care and resources may also serve as further barriers to effective self-management.

People with thalassemia and their families have adopted computer and mobile technology such as standard cell phones, smartphones, the Internet, and social networking at a rapid rate across levels of social position and status (Badawy 2016b; Lenhart 2015; Shah 2014; Smith 2015a; Ward 2016). Therefore, the widespread availability and frequent use of these technologies by those with thalassemia and their families across age groups present an opportunity to develop high-quality, efficacious, and cost-effective interventions to facilitate self-management, promote medication adherence, link people with thalassemia with their physicians, and improve health outcomes (Badawy 2016b; Leonard 2017; Shah 2014; Ward 2016). There has been growing interest and evidence to support the utilization of technology-based strategies, including mobile technology interventions, to improve medication adherence and self-management in people with chronic health conditions (Badawy 2017a; Badawy 2017b; Bonoro 2017; de Jongh 2012; Gurol-Urganci 2013; Lin 2014; Liu 2014; Pfaeffli 2016; Smith 2015b; Thakkar 2016; Whitehead 2016) including sickle cell disease (Crosby 2017; Jonassaint 2015) and thalassemia (Leonard 2017; Ward 2016), though the cost-effectiveness of such interventions warrants further investigation (Badawy 2016c). To date, the evidence for the use of computer and mobile technology interventions in people with thalassemia remains unclear. Although this systematic review may not yet identify any eligible studies, it is important to identify and report this knowledge gap

in the field of thalassemia to highlight where future research efforts can be directed using computer and mobile technology interventions.

## OBJECTIVES

To identify and assess the effects of computer and mobile technology interventions designed to facilitate medication adherence and disease management in individuals with thalassemia, including:

1. evaluating the effects of using computer and mobile technology interventions for medication adherence and disease management on health and behavioural outcomes;
2. identifying and assessing the effects of computer and mobile technology interventions specific to different age groups (children, adolescents and adults) and type of modality (e.g. cell phone, the Internet).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials (RCT) and quasi-randomized controlled trials (QRCTs) comparing single- or multi-component interventions versus no intervention, placebo or standard care. Non-randomized studies of interventions (NRSI) will also be included: controlled before-after (CBA) studies, uncontrolled pilot before-after studies, and interrupted-time-series (ITS) studies. The Cochrane Effective Practice and Organization of Care (EPOC) Group's definition of study designs will be used to consider studies for inclusion (EPOC 2017).

Given the growing evidence in the field and the possible paucity of research studies, in particular RCTs, evaluating technology interventions in this population, we wanted to broaden our eligibility criteria to be able to report the up-to-date current status of the field and identify gaps. Therefore, we are including NRSI in this review.

We will include cluster-randomized trials, non-randomized cluster trials, and CBA studies if they have at least two intervention sites and two control sites. However, we will exclude those cluster-randomized trials, non-randomized cluster trials, and CBA studies that have only one intervention or control site since the intervention (or comparison) could be confounded by the study site, thus making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables (EPOC 2017).

We will include ITS and repeated-measures studies which have a clearly defined point in time when the intervention occurred and at least three data points before and at least three data points after the intervention. We will exclude ITS studies that do not have a clearly defined point in time when the intervention occurred, fewer than three data points before and after the intervention, or if the ITS study has ignored secular (trend) changes, performed a simple t-test of the pre- versus post-intervention periods and re-analysis of the data is not possible (EPOC 2017).

We will evaluate for the possible bias introduced by confounding in the different types of included studies, and we will adjust for confounder variables. Possible confounders include age and education of the participant, self-management skills, personal behavior or personality traits, health literacy, parental involvement in medical care, parental education, household income, insurance status, access to healthcare services, type of thalassemia (transfusion-dependent versus non-transfusion-dependent thalassemia), associated co-morbidities or complications (or both) affecting clinical course, and iron chelation regimen.

Studies with a cross-over design will be excluded since any intervention focused on improving disease knowledge will leave that knowledge with a residual 'carry-over' effect, which would be difficult to assess.

### Types of participants

- People with transfusion-dependent or non-transfusion-dependent thalassaemia, all ages (children, adolescents and adults)
- Parents or caregivers of people with transfusion-dependent or non-transfusion-dependent thalassaemia

### Types of interventions

Interventions, delivered via:

- cell phones, including smartphones;
- the Internet; or
- other technology or mobile devices.

versus

- other technology interventions;
- no interventions;
- standard of care; or
- placebo.

We will include remote and Web 2.0-based interventions delivered via technologies that give people with thalassemia access to e-health information to promote medication adherence and disease management. These e-health technologies include personal computers (PCs) and applications (apps) for mobile technology such as iOS tablets (iPads), Android tablets and smartphones.

We will include e-health or technology-based interventions that are focused on people with thalassemia and parents or caregivers

to promote individual medication adherence and disease management and are self-administered or user-centred (where the intervention design process focuses on user needs).

We will also include as possible comparison groups (whenever reported): face-to-face support; educational material (either as hard copy or digital documents); or self-management tools (either as hard copy or digital documents).

We will exclude studies that focus on monitoring devices, tele-monitoring or telemedicine or other technologies that involve the participation of healthcare professionals.

### Types of outcome measures

#### Primary outcomes

1. Medication adherence, as measured by one or more of the following:
  - i) directly observed adherence rates with individuals recording their daily iron chelator use on their cell phones;
  - ii) radiological markers of iron overload (MRI of liver R2\* and MRI of heart T2\*);
  - iii) laboratory markers of iron overload (serum ferritin levels);
  - iv) iron chelators adherence rates by pharmacy records (i.e. medication possession ratio);
  - v) self-reported iron chelator adherence rate.

#### Secondary outcomes

1. Knowledge about thalassemia
2. Health outcomes (e.g. health-related quality of life)
3. User evaluation of the mobile technology interventions, including acceptability and satisfaction
4. Adverse events (e.g. issues of privacy and disclosure, or failure or delay in the intervention delivery)

### Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

#### Electronic searches

We will identify relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (thalassaemia OR (haemoglobinopathies AND general)) AND (mobile technology).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library)

and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

In addition to the above, we will conduct a search of the following databases:

- CENTRAL, Other Reviews (DARE) and Technology Assessments (HTA) Databases (the Cochrane Library, current issue) ([www.cochranelibrary.com/](http://www.cochranelibrary.com/));
- PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, for recent records not yet added to MEDLINE) ([www.ncbi.nlm.nih.gov/sites/entrez](http://www.ncbi.nlm.nih.gov/sites/entrez));
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to present);
- Embase (OvidSP, 1974 to present);
- CINAHL (EBSCOHost, 1937 to present);
- PsycInfo (EBSCOHost, 1900 to present);
- ProQuest Dissertations & Theses Global (ProQuest, 1861 to present);
- Web of Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 to current);
- Institute of Electrical and Electronics Engineers Explore (IEEE Xplore, 1963 to present)

Additionally, we will search the following trial databases for trials:

- ISRCTN registry ([www.isrctn.com/](http://www.isrctn.com/));
- ClinicalTrials.gov ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov));
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)).

See [Appendix 1](#) for the full search strategies.

### Searching other resources

We will further aim to identify unpublished work by searching the abstract books of the International Society for Research on Internet interventions (ISRII); the NIH Wireless Health conference; the Society for Behavioral Medicine (SBM) annual meeting; and the Connected Health conference over the past 10 years (2007 to 2017).

### Reference lists

The reference lists of all included articles and relevant systematic reviews will be reviewed to identify any additional studies. We

will contact the lead authors of the included studies to identify any unpublished material, missing data or information regarding ongoing relevant studies.

## Data collection and analysis

### Selection of studies

We will select studies according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). Two review authors (SB and KM) will independently screen all electronically derived citations and abstracts of papers identified by the search strategy for relevance. We will exclude all articles that are clearly irrelevant at this stage based on the title and the abstract. Two review authors (SB and KM) will independently assess the full texts of all potentially relevant trials or studies for eligibility against criteria outlined above. If a consensus cannot be reached, we aim to resolve any disagreements by discussion and consultation with a third review author (TP). We will seek further information from study authors if studies or abstracts contain insufficient data to make a decision about eligibility. We will design a study eligibility form which will include ascertaining whether the participants have thalassaemia, if the study addresses mobile technology interventions to improve disease management, and whether the study design is randomized or NRSI or a CBA or an ITS study. We will also record the reasons why potentially relevant studies failed to meet the eligibility criteria.

### Data extraction and management

Two review authors (SB and KM) will conduct data extraction according to Cochrane guidelines ([Higgins 2011a](#)) and according to the criteria developed for NRSI as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* ([Reeves 2011](#)). We aim to resolve any disagreements by consensus. We will pilot data extraction forms for RCTs, NRSI or CBAs or ITS studies; thereafter, data extraction will be conducted by two authors (SB and KM) independently for all the studies using templates modified to reflect the outcomes in this review. In addition, we will use the available tables in Review Manager 5 ([RevMan 2014](#)) to extract data on study characteristics as below.

### General information

Review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, and objectives of the study.

### Study details

Study design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

### Characteristics of participants

Age, gender, total number recruited, total number randomized, total number analyzed, types of underlying disease, loss to follow-up numbers, dropouts (percentage in each arm) with reasons, protocol violations (if any), and co-morbidities.

### Interventions

Details of the mobile technology interventions including purpose (e.g. adherence promotion), modality used (cell phone, the Internet or other technology), length of intervention, how the intervention is being delivered (i.e. electronically only or electronically in addition to group, face-to-face, written information) and by whom (i.e. clinicians, researchers, patients or parents) and where the intervention is being delivered (i.e. hospital, clinic, home or other settings). Data from different modes of interventions will be analysed separately (e.g. cell phone versus standard care, Internet versus standard care, etc.).

### Outcomes measured

We will collect data on measures of medication adherence, including iron chelators adherence rates by self-report or pharmacy records (or both) (i.e. medication possession ratio), laboratory markers of iron overload (serum ferritin level), radiological markers of iron overload (MRI of liver R2\* and MRI of heart T2\*), and other reported adherence indicators. We will also collect data on knowledge about thalassemia and health outcomes (e.g. health-related quality of life).

We will also collect data on user perception of acceptability and satisfaction (e.g. the Likert ratings of satisfaction). Adverse events will be extracted if they are reported and we will note whether or not they are associated with interventions.

For NRSI, CBA or ITS studies, data will be collected, if available, on: confounding factors; the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011). Both full-text versions and abstracts will be used as data sources and use one data extraction form for each unique study. Where sources do not provide sufficient information, authors and study groups will be contacted for additional details. Data will be entered by one review author then checked for accuracy by a second review author.

### Assessment of risk of bias in included studies

All included studies will be assessed by two review authors (SB and TP) for possible risks of bias as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c). In our assessment, we will include information about the design, the conduct and the analysis of the study.

### RCTs

Each criterion will be assessed using Cochrane's RoB (V2.0) tool for assessing the risk of bias for RCTs (classified as 'low risk', 'high risk' or 'some concerns' for bias) in the following areas.

### Bias arising from the randomization process

1. Was the allocation sequence random?
2. Was the allocation sequence concealed until participants were recruited and assigned to interventions?
3. Were there baseline imbalances that suggest a problem with the randomization process?
4. What is the predicted direction of bias arising from the randomization process?

### Bias due to deviations from intended interventions

1. Were participants aware of their assigned intervention during the trial?
2. Were carers and trial personnel aware of participants' assigned intervention during the trial?
3. Were there deviations from the intended intervention beyond what would be expected in usual practice?
4. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?
5. Were any participants analysed in a group different from the one to which they were assigned?
6. Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?
7. What is the predicted direction of bias due to deviations from intended interventions?

### Bias due to missing outcome data

1. Were outcome data available for all, or nearly all, participants randomized?
2. Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?
3. Is there evidence that results were robust to the presence of missing outcome data?
4. What is the predicted direction of bias due to missing outcome data?

### **Bias in measurement of the outcome**

1. Were outcome assessors aware of the intervention received by study participants?
2. Was the assessment of the outcome likely to be influenced by knowledge of intervention received?
3. What is the predicted direction of bias due to measurement of the outcome?

### **Bias in selection of the reported result(s)**

1. Are the reported outcome data likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain? Or from multiple analyses of the data?
2. What is the predicted direction of bias due to selection of the reported result?

### **Overall bias**

### **NRSI studies**

The ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) will be used to rate the quality of NRSI or CBA studies (Sterne 2016). The ROBINS-I tool uses signalling questions and covers seven domains (listed below) where the quality of evidence is rated as 'low', 'moderate', 'serious', 'critical' or 'no information'.

### **Bias due to confounding**

1. Is there potential for confounding of the effect of intervention in this study?
2. Was the analysis based on splitting participants' follow-up time according to intervention received?
3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?
4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?
5. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
6. Did the authors control for any post-intervention variables that could have been affected by the intervention?
7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time varying confounding?
8. Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?

### **Bias in the selection of participants into the study**

1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?
2. Were the post-intervention variables that influenced selection likely?
3. Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?
4. Do start of follow-up and start of intervention coincide for most participants?

### **Bias in classification of interventions**

1. Were intervention groups clearly defined?
2. Was the information used to define intervention groups recorded at the start of the intervention?
3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
4. What is the predicted direction of bias due to measurement of outcomes or interventions?

### **Bias due to deviation from intended interventions**

1. Were there deviations from the intended intervention beyond what would be expected in usual practice?
2. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?
3. Were important co-interventions balanced across intervention groups?
4. Was the intervention implemented successfully for most participants?
5. Did study participants adhere to the assigned intervention regimen?
6. Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?
7. What is the predicted direction of bias due to deviations from the intended interventions?

### **Bias due to missing data**

1. Were outcome data available for all, or nearly all, participants?
2. Were participants excluded due to missing data on intervention status?
3. Were participants excluded due to missing data on other variables needed for the analysis?
4. Are the proportion of participants and reasons for missing data similar across interventions?
5. Is there evidence that results were robust to the presence of missing data?

6. What is the predicted direction of bias due to missing data?

### Bias in measurement of outcomes

1. Could the outcome measure have been influenced by knowledge of the intervention received?
2. Were outcome assessors aware of the intervention received by study participants?
3. Were the methods of outcome assessment comparable across intervention groups?
4. Were any systematic errors in measurement of the outcome related to intervention received?
5. What is the predicted direction of bias due to measurement of outcomes?

### Bias in the selection of the reported result

1. Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain? Or from multiple analyses of the intervention outcome relationship? Or from different subgroups?
2. What is the predicted direction of bias due to selection of the reported result?

### ITS studies

For ITS studies, the risk of bias criteria below will be used as suggested for EPOC reviews (EPOC 2017) as follows.

- Was the intervention independent of other changes?
- Was the shape of the intervention effect pre-specified?
- Was the intervention unlikely to affect data collection?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Was the study free from selective outcome reporting?
- Was the study free from other risks of bias?

### Cross-over trials

For cross-over trials, the risk of bias will be assessed across the following domains (Higgins 2011c).

- Suitability of the cross-over design
- Evidence of a carry-over effect
- Whether only first period data were available
- Incorrect statistical analysis
- Comparability of results with those from randomized trials

We will aim to resolve disagreements on the assessment of quality of an included study by discussion until consensus is reached or by consultation with a third review author (KM or AT).

## Measures of treatment effect

### RCTs

We expect to report the following continuous primary endpoints of medication adherence, including iron chelators adherence rates by self-report, iron chelators adherence rates by pharmacy records (i.e. medication possession ratio, laboratory markers of iron overload with serum ferritin level, radiological markers of iron overload (MRI of liver R2\* and MRI of heart T2\*), and other reported adherence indicators. We also expect to report the following continuous secondary endpoints (user evaluation of acceptability and satisfaction). For continuous endpoints, we plan to extract and report the absolute change from baseline using statistical analysis, adjusting for baseline differences, in both the treatment and control groups. We will record the mean, standard deviation (SD) and total number of participants in both the treatment and control groups. For those using the same scale or outcome, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For those reported using different scales or outcomes, we will use the standardized mean difference (SMD). We will extract and report the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups divided by the post-intervention level in the control group) (EPOC 2017).

For cluster-randomized studies, we will extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis with necessary adjustment using effective sample size recalculation, following the recommendations in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

If data allow, we will undertake quantitative assessments using the Review Manager (RevMan) software (RevMan 2014).

### NRSI studies

For continuous variables in the included studies, if available, we will extract and report the absolute change from baseline using statistical analysis, adjusting for baseline differences (such as regression models, mixed models or hierarchical models). An adjusted change of outcomes is required in NRSI and confounding will be considered and evaluated in the included articles. If available, we will extract and report the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups divided by the post-intervention level in the control group) (EPOC 2017).

## ITS studies

For ITS studies that fulfil the criteria of analysis, and from which relevant information can be extracted, we will standardize data by dividing the level (or time slope) and standard error (SE) by the SD of the pre-intervention slope, in order to obtain the effect sizes. Where appropriate, we will report the number-needed-to-treat-to-benefit (NNTB) and the number-needed-to-treat-to-harm (NNTH) with 95% CIs. If we are not able to report the available data in any of the formats described above, we will produce a narrative report, and if appropriate, we will present the data in tables.

## Unit of analysis issues

We expect to identify issues related to units of analysis, given the inclusion of cluster randomized studies or non-randomized studies, and multiple observations for the same outcome. Therefore, if any of these study designs will be included in our review, we will treat these in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). For cluster designs, we will extract results adjusted for clustering, and if analyses have not been adjusted for clustering, we will re-analyze the data taking clustering and individual participant data (IPD) into account, if such an analysis is possible. If adjustment is not possible, we will present data in a table. If participants are randomized more than once, we will contact the authors of the study to provide us with data on outcomes associated with the initial randomization. For studies with multiple treatment groups, we will include subgroups that are considered relevant to the analysis. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and the others will be excluded (Higgins 2011d). We will deal with any unit of analysis issues arising from the inclusion of ITS studies according to the EPOC recommendations (EPOC 2017). The preferred method to analyze ITS studies is a statistical comparison of time trends before and after the intervention. In time-series analysis, there are a number of statistical techniques that can be used depending on the characteristics of the data, the number of data points available and whether autocorrelation is present (e.g. auto-regressive integrated moving average 'ARIMA' model).

## Dealing with missing data

If we identify incidences where we suspect data are missing or unclear, we will contact study authors directly. We will record the number of participants lost to follow-up for each study. Where possible, we will analyze data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per protocol analyses (Higgins 2011c).

## Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will analyze the data from RCTs, NRSI, CBA and ITS studies separately. We will assess the statistical heterogeneity of treatment effects between studies using a Chi<sup>2</sup> test with a significance level at  $P < 0.1$ . We will use the I<sup>2</sup> statistic to quantify the degree of potential heterogeneity and classify it as moderate if I<sup>2</sup> is greater than 50%, or considerable if I<sup>2</sup> is greater than 75%. If statistical heterogeneity is moderate within the studies selected for inclusion; in such cases, we will use the random-effects model. If statistical heterogeneity is considerable within the studies selected for inclusion, we will not report the overall summary statistic. When possible, we will assess the potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

## Assessment of reporting biases

Where at least 10 studies identified for inclusion in a meta-analysis, potential publication bias will be explored with a funnel plot and using a linear regression test. We will consider a P-value of less than 0.1 as significant for this test (Sterne 2011).

## Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to Cochrane recommendations (Deeks 2011). We will analyze RCTs and non-RCTs separately using the random-effects model as the true effects are expected to be related but not the same for included studies. If we cannot perform a meta-analysis, we will include a narrative describing the results and the results from all studies will be presented in tables. For RCTs, where meta-analysis is feasible, we will use the inverse variance method for continuous outcomes, or outcomes that include data from cluster-RCTs. If we find heterogeneity to be above 75%, and a cause for the heterogeneity was identified, we will explore further with subgroup analyses. If a cause for the heterogeneity cannot be found, then we will not perform a meta-analysis. If meta-analysis is feasible for NRSI or CBA studies, we will analyze these separately. We will only analyze outcomes with adjusted effect estimates, if these are adjusted for the same factors using the inverse variance method as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

If meta-analysis is feasible for ITS studies, we will use the effect sizes (if reported in the included studies or obtained, as described earlier) and we will pool these using the generic inverse variance method in RevMan (RevMan 2014). We will report data for our listed outcomes at the following time points: pre-intervention, immediate post-intervention and at first follow up (up to 12 months).

## Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses according to Cochrane recommendations (Deeks 2011) for each of the following criteria, and separately for the different study design types included in the review in order to assess the effect on heterogeneity. We will base the subgroup analysis on:

1. delivery mode, phone-based versus Internet-based interventions;
2. age groups, children (8 to 11 years old) (parent-focused) versus adolescents (12 to 17 years old) versus adults (18 years and above);
3. transfusion-dependent versus non-transfusion-dependent thalassemia; and
4. iron-chelation regimen, deferasirox versus deferoxamine versus deferiprone.

## Sensitivity analysis

We will assess the robustness of the review findings by performing the following sensitivity analyses according to Cochrane recommendations where appropriate (Deeks 2011):

- including only those studies with a 'low' risk of bias (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation);
- including only those studies with less than a 20% dropout rate.

## Summary of findings table

We will use the GRADE approach to generate a 'Summary of Findings' table as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a). We will rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations.

- Risk of Bias (serious or very serious)
- Inconsistency (serious or very serious)

- Indirectness (serious or very serious)
- Imprecision (serious or very serious)
- Publication bias (likely or very likely)

For non-RCTs or CBA or ITS studies, the following factors will also be considered:

- dose response (yes or no);
- size of effect (large or very large);
- confounding either reduces the demonstrated effect or increases the effect if no effect was observed (yes or no)

In GRADE, we will initially rate NRSI or CBA or ITS studies as low quality and upgraded according to GRADE guidelines if appropriate. We will present the outcomes for these studies in separate tables from outcomes for the results of RCTs. We will report the following outcomes in each 'Summary of findings' table:

1. directly observed adherence rates with individuals recording their daily iron chelator use on their cell phones;
2. radiological markers of iron overload (MRI of liver R2\* and MRI of heart T2\*);
3. laboratory markers of iron overload (serum ferritin levels);
4. iron chelators adherence rates by pharmacy records (i.e. medication possession ratio);
5. self-reported iron chelator adherence rate;
6. disease knowledge about thalassemia; and
7. health outcomes (e.g. health-related quality of life).

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. Search Methods - Electronic Searching

Database/ Resource	Strategy
CENTRAL, DARE and HTA Databases (via the Cochrane Library, all years)	<p>#1 MeSH descriptor: [Thalassemia] explode all trees</p> <p>#2 Thalass*mia*</p> <p>#3 alpha-thal*</p> <p>#4 beta-thal*</p> <p>#5 delta-thal*</p> <p>#6 #1 or #2 or #3 or #4 or #5</p> <p>#7 MeSH descriptor: [Cell Phones] explode all trees</p> <p>#8 (Cellphone* or ((cell* or mobile) and (Phone* or telephone*) or iphone*))</p> <p>#9 MeSH descriptor: [Microcomputers] explode all trees</p> <p>#10 MeSH descriptor: [Mobile Applications] this term only</p> <p>#11 (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps)</p> <p>#12 ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*))</p> <p>#13 MeSH descriptor: [Internet] explode all trees</p> <p>#14 MeSH descriptor: [Computer Simulation] this term only</p> <p>#15 MeSH descriptor: [Electronic Mail] this term only</p> <p>#16 MeSH descriptor: [Reminder Systems] this term only</p> <p>#17 MeSH descriptor: [Wireless Technology] this term only</p> <p>#18 MeSH descriptor: [Software] explode all trees</p> <p>#19 (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based)</p> <p>#20 (wireless AND (technolog* OR communicat*))</p> <p>#21 MeSH descriptor: [Video Recording] this term only</p> <p>#22 MeSH descriptor: [Videoconferencing] explode all trees</p> <p>#23 MeSH descriptor: [Telemedicine] explode all trees</p> <p>#24 MeSH descriptor: [Text Messaging] this term only</p> <p>#25 (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service)</p> <p>#26 (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*)</p> <p>#27 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26</p> <p>#28 #6 and #27</p>

(Continued)

<p><b>PubMed</b></p>	<p>(Thalassemia[tw] OR Thalassemias[tw] or <math>\alpha</math>-thalassemia[tw] OR <math>\alpha</math>-thalassemias[tw] OR <math>\alpha</math>-thal[tw] or alpha-thalassemia[tw] OR alpha-thalassemias[tw] OR <math>\beta</math>-thalassemia[tw] OR <math>\beta</math>-thalassemias[tw] OR <math>\beta</math>-thal[tw] OR beta-thalassemia[tw] OR beta-thalassemias[tw] OR <math>\delta</math>-thalassemia[tw] OR <math>\delta</math>-thalassemias[tw] OR <math>\delta</math>-thal[tw] OR delta-thalassemia[tw] OR delta-thalassemias[tw] OR Thalassaemia[tw] OR Thalassemias[tw] or <math>\alpha</math>-thalassaemia[tw] OR <math>\alpha</math>-thalassaemias[tw] OR <math>\alpha</math>-thal[tw] or alpha-thalassaemia[tw] OR alpha-thalassaemias[tw] OR <math>\beta</math>-thalassaemia[tw] OR <math>\beta</math>-thalassaemias[tw] OR <math>\beta</math>-thal[tw] OR beta-thalassaemia[tw] OR beta-thalassaemias[tw] OR <math>\delta</math>-thalassaemia[tw] OR <math>\delta</math>-thalassaemias[tw] OR <math>\delta</math>-thal[tw] OR delta-thalassaemia[tw] OR delta-thalassaemias[tw])</p> <p>AND ("mobile health"[tw] OR "mhealth"[tw] OR "ehealth"[tw] OR "m-health"[tw] OR "e-health"[tw] OR "mcare"[tw] OR "cell-phone"[tw] OR "cellphones"[tw] OR "cell phones"[tw] OR "cell phone" OR "cellular phone"[tw] OR "cellular phones"[tw] OR "cellular telephone"[tw] OR "cellular telephones"[tw] OR "mobile phone"[tw] OR "mobile phones"[tw] OR "mobile telephone"[tw] OR "mobile telephones"[tw] OR "iphone"[tw] OR "iphones"[tw] OR "microcomputer"[tw] OR "microcomputers"[tw] OR "handheld computer"[tw] OR "handheld computers"[tw] OR "hand held computer"[tw] OR "hand held computers"[tw] OR "ipad"[tw] OR "ipads"[tw] OR "pda"[tw] OR "pdas"[tw] OR "personal digital assistant"[tw] OR "personal digital assistants"[tw] OR "blackberry"[tw] OR "android"[tw] OR "androids"[tw] OR "smartphone"[tw] OR "smartphones"[tw] OR "smart phone"[tw] OR "smart phones"[tw] OR "tablet"[tw] OR "apps"[tw] OR "app"[tw] OR "mobile application"[tw] OR "mobile applications"[tw] OR "mobile communication"[tw] OR "mobile communications"[tw] OR "mobile technology"[tw] OR "mobile technologies"[tw] OR "mobile game"[tw] OR "mobile games"[tw] OR "internet"[tw] OR "computer simulation"[tw] OR "email"[tw] OR "emails"[tw] OR "emailing"[tw] OR "e-mail"[tw] OR "e-mails"[tw] OR "e-mailing"[tw] OR "electronic mail"[tw] OR "reminder systems"[tw] OR "reminder system"[tw] OR "wireless technology"[tw] OR "wireless technologies"[tw] OR "wireless communication"[tw] OR "wireless communications"[tw] OR "software"[tw] OR "video recording"[tw] OR "video recordings"[tw] OR teleconference*[tw] OR "text message"[tw] OR "text messaging"[tw] OR "texting"[tw] OR "text"[tw] OR "texts"[tw] OR "SMS"[tw] OR "short message service"[tw] OR "text messages"[tw] OR "Handheld device"[tw] OR "handheld devices"[tw] OR "mobile tool"[tw] OR "mobile tools"[tw] OR "electronic device"[tw] OR "electronic devices"[tw] OR "electronic tool"[tw] OR "electronic tools"[tw] OR "electronic health"[tw] OR "electronic monitoring"[tw] OR "e-</p>
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	monitoring"[tw] OR "electronically monitor"[tw] OR "electronic mentoring"[tw] OR "telehealth"[tw] OR "telehealthcare"[tw] OR "telemonitoring"[tw] OR "telementoring"[tw] OR "telecare"[tw] OR "telemedicine"[tw] OR "telecommunication"[tw] OR "telecommunications"[tw] OR "videoconferencing"[tw] OR "videoconference"[tw] OR "bluetooth"[tw] OR "web-based"[tw]
<b>MEDLINE (OvidSP, 1946 to present)</b>	<ol style="list-style-type: none"> <li>1. exp Thalassemia/</li> <li>2. Thalass?emia*.af.</li> <li>3. alpha-thal*.af.</li> <li>4. beta-thal*.af.</li> <li>5. delta-thal*.af.</li> <li>6. 1 or 2 or 3 or 4 or 5</li> <li>7. exp Cell Phones/</li> <li>8. (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*).af</li> <li>9. exp Microcomputers/</li> <li>10. Mobile Applications/</li> <li>11. (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps).af</li> <li>12. ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)).af</li> <li>13. exp Internet/</li> <li>14. Computer Simulation/</li> <li>15. Electronic mail/</li> <li>16. Reminder Systems/</li> <li>17. Wireless Technology/</li> <li>18. exp Software/</li> <li>19. (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based).af</li> <li>20. (wireless AND (technolog* OR communicat*)).af.</li> <li>21. Video Recording/</li> <li>22. exp Videoconferencing/</li> <li>23. exp Telemedicine/</li> <li>24. Text Messaging/</li> <li>25. (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service).af</li> <li>26. (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*).af</li> <li>27. or/7-26</li> <li>28. 6 and 27</li> </ol>

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<b>Embase (OvidSP, 1974 to present)</b>	1. exp Thalassemia/ 2. Thalass?emia*.af. 3. alpha-thal*.af. 4. beta-thal*.af. 5. delta-thal*.af. 6. 1 or 2 or 3 or 4 or 5 7. exp Mobile Phone/ 8. (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*).af 9. Microcomputer/ 10. Mobile Application/ 11. (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps).af 12. ((mobile or electronic* or handheld or hand-held) and (ap- plication* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*))).af 13. Internet/ 14. Computer Simulation/ 15. E-mail/ 16. Reminder System/ 17. Wireless Communication/ 18. Software/ 19. (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based).af 20. (wireless AND (technolog* OR communicat*))).af. 21. Videorecording/ 22. Videoconferencing/ 23. exp Telemedicine/ 24. Text Messaging/ 25. (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service) .af 26. (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*).af 27. or/7-26 28. 6 and 27
<b>CINAHL (EBSCOHost, 1937 to present)</b>	S1 MH thalassemia S2 TX thalass#emia* S3 TX alpha-thal* S4 TX beta-thal* S5 TX delta-thal* S6 S1 OR S2 OR S3 OR S4 OR S5 S7 (MH "Cellular Phone") OR (MH "Smartphone") S8 TX Cellphone* or ((cell* or mobile) and (Phone* or tele-

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	<p>phone*) or iphone*</p> <p>S9 (MH "Microcomputers") OR (MH "Computers, Portable+")</p> <p>S10 (MH "Mobile Applications")</p> <p>S11 TX Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps</p> <p>S12 TX (mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*)</p> <p>S13 (MH "Internet")</p> <p>S14 (MH "Computer Simulation")</p> <p>S15 (MH "Electronic Mail")</p> <p>S16 (MH "Reminder Systems")</p> <p>S17 (MH "Wireless Communications")</p> <p>S18 (MH "Software") OR (MH "Communications Software")</p> <p>S19 TX internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based</p> <p>S20 TX wireless AND (technolog* OR communicat*)</p> <p>S21 (MH "Videorecording") OR (MH "Videoconferencing+")</p> <p>S22 (MH "Telecommunications+") OR (MH "Telehealth+")</p> <p>S23 TX video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service</p> <p>S24 TX mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*</p> <p>S25 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24</p> <p>S26 S6 AND S25</p>
<b>PsycInfo (EBSCOHost, 1900 to present)</b>	<p>S1 TX thalass#emia*</p> <p>S2 TX alpha-thal*</p> <p>S3 TX beta-thal*</p> <p>S4 TX delta-thal*</p> <p>S5 S1 OR S2 OR S3 OR S4</p> <p>S6 DE "Mobile Devices" OR DE "Cellular Phones" OR DE "Electronic Communication" OR DE "Blog" OR DE "Computer Mediated Communication" OR DE "Electronic Learning" OR DE "Social Media" OR DE "Text Messaging"</p> <p>S7 TX Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*</p> <p>S8 DE "Microcomputers"</p> <p>S9 TX Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps</p> <p>S10 TX (mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool*</p>

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	<p>or device* or monitor* or mentor* or computer*)</p> <p>S11 DE "Internet"</p> <p>S12 DE "Computer Simulation"</p> <p>S13 DE "Computer Software" OR DE "Groupware"</p> <p>S14 TX internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based</p> <p>S15 TX wireless AND (technolog* OR communicat*)</p> <p>S16 DE "Teleconferencing" OR DE "Telemedicine"</p> <p>S17 TX video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service</p> <p>S18 TX mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*</p> <p>S19 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18</p> <p>S20 S5 AND S19</p>
<b>Web of Science &amp; Social Sciences Conference Proceedings Indexes (CPSI-S &amp; CPSSI, 1990 to current)</b>	<p>#1 TOPIC: (Thalass*emia*)</p> <p>#2 TOPIC: (alpha-thal*)</p> <p>#3 TOPIC: (beta-thal*)</p> <p>#4 TOPIC: (delta-thal*)</p> <p>#5 #4 OR #3 OR #2 OR #1</p> <p>#6 TOPIC: (Cellphone* or ((cell* or mobile) and (Phone* or telephone*)) or iphone*)</p> <p>#7 TOPIC: (Microcomputer* or ipad* or pda* or personal digital assistant* or blackberry* or android* or smartphone* or smart phone* or tablet or app or apps)</p> <p>#8 TOPIC: ((mobile or electronic* or handheld or hand-held) and (application* or communication* or technolog* or game* or tool* or device* or monitor* or mentor* or computer*))</p> <p>#9 TOPIC: (internet OR computer simulation OR email* OR e-mail* OR electronic mail OR remind* system* OR software OR Bluetooth OR web-based)</p> <p>#10 TOPIC: (wireless AND (technolog* OR communicat*))</p> <p>#11 TOPIC: (video recording* or videoconference* or teleconference* or texting or texts or text message* or SMS or short messag* service)</p> <p>#12 TOPIC: (mobile health or mhealth or ehealth or m-health or e-health or mcare or electronic health or e-monitoring or telehealth* or telemonitoring or telementoring or telecare or telemedicine or telecommunication*)</p> <p>#13 #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6</p> <p>#14 #13 AND #5</p>
<b>Institute of Electrical and Electronics Engineers Explore (IEEE Xplore, 1963 to present)</b>	<p>thalassemia OR thalassemia</p>

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ISRCTN registry	thalassemia OR thalassaemia
ClinicalTrials.gov [new search interface]	Condition/ Disease: thalassemia Other terms: phone OR smartphone OR computer OR mobile OR electronic OR app OR game OR wireless OR email OR video OR text OR sms OR video OR electronic OR internet OR web OR device OR technology OR Bluetooth OR online OR remote OR monitor OR communication OR telecommunication OR teleconference OR videoconference OR videoconferencing OR teleconference OR teleconferencing
WHO International Clinical Trials Registry Platform (ICTRP)	[Advanced Search Form] Condition: thalassemia OR thalassaemia Intervention: phone OR smartphone OR computer OR mobile OR electronic OR app OR game OR wireless OR email OR video OR text OR sms OR video OR electronic OR internet OR web OR device OR technology OR Bluetooth OR online OR remote OR monitor OR communication OR telecommunication OR teleconference OR videoconferenc* OR teleconference* Recruitment Status: All

## CONTRIBUTIONS OF AUTHORS

Sherif Badawy: conceiving the review, protocol development, methodological expert and content expert.

Kerry Morrone: protocol development and content expert.

Alexis Thompson: protocol development and content expert.

Tonya Palermo: protocol development and methodological expert.

## DECLARATIONS OF INTEREST

All authors: none known.

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- No sources of support supplied

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